



# Genetic and clinical characteristics of hereditary transthyretin amyloidosis in endemic and non-endemic areas: experience from a single-referral center in Japan

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## Abstract

Hereditary transthyretin (ATTR) amyloidosis is a life-threatening, autosomal dominant, systemic amyloidosis caused by mutant transthyretin. In addition to ATTRV30M in endemic and non-endemic areas, more than 140 non-V30M mutations occur worldwide. The aim of this study was to analyze the clinical characteristics and genetic frequencies of hereditary ATTR amyloidosis. Diagnostic results and clinical manifestations of hereditary ATTR amyloidosis from April 1, 2012, to March 31, 2017, at Amyloidosis Medical Practice Center, Kumamoto University Hospital were analyzed. One hundred and four patients received a diagnosis of symptomatic hereditary ATTR amyloidosis. The following mutations of the TTR gene and their percentages were found: V30M in endemic areas, 10.6%; V30M in non-endemic areas, 51.0%; and non-V30M, 38.5%. The ages at onset of patients with ATTRV30M amyloidosis in non-endemic areas ( $66.6 \pm 8.7$  years) and those with non-V30M ATTR amyloidosis ( $55.8 \pm 13.6$  years) were significantly higher than those with ATTRV30M amyloidosis in endemic areas ( $37.0 \pm 12.6$  years). Of patients with ATTRV30M amyloidosis in endemic and non-endemic areas, and non-V30M ATTR amyloidosis, 63.6, 66.0, and 27.5% initially presented with polyneuropathy, respectively. Of patients with ATTRV30M amyloidosis in endemic areas, 81.8% had a family history of this disease. However, a significantly smaller percentage of patients with ATTRV30M amyloidosis (30.0%) in non-endemic areas and non-V30M ATTR amyloidosis (34.0%) had a family history. Patients with ATTRV30M amyloidosis in non-endemic areas and patients with non-V30M ATTR amyloidosis occurred more frequently than previously believed, and their clinical manifestations were diverse.

**Keywords** Amyloidosis · Transthyretin · Mutations · Diagnosis · Endemic area

## Introduction

Amyloidosis comprises a large group of disorders caused by accumulation of proteins in the form of abnormal and insoluble fibers, called amyloid fibrils, in the extracellular space of organs including the peripheral nerves, heart, kidneys, eyes, brain, and others [1]. After a steady increase in the number of human amyloid proteins, 36 are now known. Hereditary transthyretin (ATTR) amyloidosis (transthyretin-type familial amyloid polyneuropathy, ATTR-FAP) is a life-threatening, autosomal dominant, systemic amyloidosis caused by mutant transthyretin (TTR) [2, 3]. Patients with a mutation in the *TTR* gene that result in normal valine and variant methionine (ATTRV30M, p.TTRV50M, c.148G>A) are found most commonly, and large endemic areas of this disease have been reported in Portugal, Sweden, and Japan

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[4–6]. In addition, more than 140 non-V30M mutations have been reported in non-endemic areas in the world [7, 8].

Clinical manifestations in the patients are highly heterogeneous and, in ATTR-FAP, include primarily presentations consisting of length-dependent peripheral sensorimotor polyneuropathy, familial amyloid cardiomyopathy, and familial oculoleptomeningeal amyloidosis, with various geographic distributions and degrees of amyloidogenesis and patterns of amyloid deposition [2, 9]. Recently, disease-modifying therapies for hereditary ATTR amyloidosis, such as liver transplantation, gene silencing with small interfering RNA to reduce production of mutant TTR by the liver, and TTR stabilizers to reduce amyloid formation, have been developed and applied to practical use or are undergoing trials [10–17]. However, early intervention with early diagnosis is often difficult, because this disease is frequently difficult to identify as a result of its clinical phenotypic heterogeneity [18].

The study described here aimed to analyze the clinical characteristics and genetic frequency of hereditary ATTR amyloidosis in patients diagnosed at the Amyloidosis Medical Practice Center, Kumamoto University Hospital, which, as a diagnostic center for amyloidosis in Japan, conducts histopathological, genetic, and proteomic analyses.

## Methods

### Patients

We analyzed the diagnostic results for patients with hereditary ATTR amyloidosis who were treated at the Amyloidosis Medical Practice Center, Kumamoto University Hospital, from April 1, 2012, to March 31, 2017. During this 5-year study period, 470 patients underwent diagnostic tests, and 104 received a diagnosis of symptomatic hereditary ATTR amyloidosis. In addition, we compared the clinical features of these 24 patients with those of patients in endemic areas who were diagnosed with ATTRV30M amyloidosis from January 1, 2000, to March 31, 2012.

### Methods

Genetic analysis was performed by purifying genomic DNA from blood leukocytes and sequencing the *TTR* gene (both forward and reverse sequences). Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry was also performed with serum TTR to detect any variant TTR peak with an increased mass, in addition to the wild-type TTR peak [19, 20].

Clinical features including sex, age at onset of disease, origin in endemic or non-endemic areas, family history,

initial manifestations, duration between the onset of disease and diagnosis, having had liver transplantation, and genotype were examined. The clinical onset of the disease was defined as the development of symptoms that are characteristic of hereditary ATTR amyloidosis and as the deposition of ATTR amyloid as determined by histopathological examinations of tissues.

Mutations were described using amino acid codes and sequence numbers of the mature proteins as recommended in studies of amyloid protein [1]. For example, p.TTRV50M (c.148G>A) was indicated by V30M.

### Statistical analysis

We analyzed the differences by means of Fisher's exact test or non-parametric Dunnett's multiple comparison test. Data were presented as means  $\pm$  standard deviations (median, minimum–maximum). Differences with a *P* value of less than 0.05 were considered statistically significant.

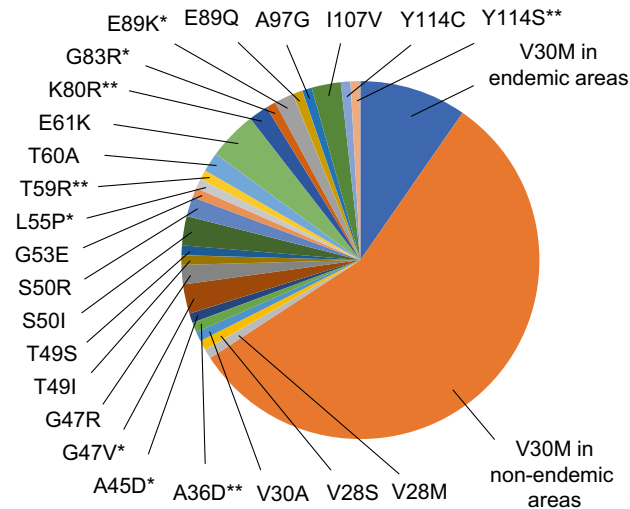
### Standard protocol approval

This Institutional Review Board of the Graduate School of Medical Sciences, Kumamoto University (No. 1172, 1387) approved this study. All patients gave their informed consent prior to their inclusion in this study.

## Results

The following mutations of the *TTR* gene were found in the 104 study patients with a diagnosis of symptomatic hereditary ATTR amyloidosis: V30M (p.TTRV50M), V28M, V28S, V30A, A36D\*\*, A45D\*, G47V\*, G47R, T49I, T49S, S50I, S50R, G53E, L55P\*, T59R\*\*, T60A, E61K, K80R\*\*, G83R\*, E89K\*, E89Q, A97G, I107V, Y114C, Y114S\*\* (\* indicates that these were the first cases in Japan; \*\*, the first cases in the world) (Fig. 1). Two patients were homozygotic for V30M and 1 was compound heterozygotic for K80R and V30M in non-endemic areas. One patient (V30M) was from Brazil and 3 patients (V28S, V30A, G83R) were from China. V30M in non-endemic areas was the most common type of mutation. Of all patients, 11 patients (10.6%) were identified as having the V30M mutation in endemic areas; 53 (51.0%) and 40 (38.5%) patients were identified as having the V30M mutation in non-endemic areas and as having non-V30M mutations, respectively. The patient who had a compound heterozygotic mutation for K80R and V30M was included with the patients with non-V30M mutations.

The differences in molecular weight as indicated by peaks for wild-type TTR and variant TTRs detected by mass spectrometry were consistent with the differences in molecular



**Fig. 1** Mutations in the TTR Gene. \*The first cases in Japan; \*\*the first cases in the world

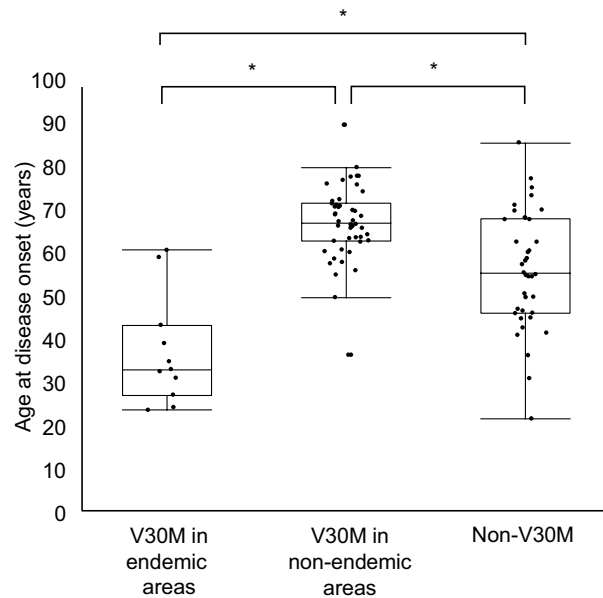
weight as estimated from the amino acid substitutions and indicated by the DNA sequences (data not shown).

Patients with ATTRV30M amyloidosis in endemic areas were mainly early-onset cases, with the age at onset of disease being  $37.0 \pm 12.6$  years (median 32.9, range 23.5–60.4). The age at onset of patients with ATTRV30M amyloidosis in non-endemic areas was  $66.6 \pm 8.7$  years (median 66.7, range 36.2–89.3) and that of patients with non-V30M ATTR amyloidosis was  $55.8 \pm 13.6$  years (median 55.0, range 21.5–85.2). These ages were significantly higher than those of patients with ATTRV30M amyloidosis in endemic areas ( $P < 0.05$ ) (Fig. 2).

The male–female ratio of patients with ATTRV30M amyloidosis in endemic areas was 0.8:1, whereas a male predominance was observed for patients with ATTRV30M amyloidosis in non-endemic areas (ratio of 4.3:1) and for patients with non-V30M ATTR amyloidosis (ratio of 1.7:1) (Fig. 3).

Of patients with ATTRV30M amyloidosis in endemic areas, 81.8% had a family history of this disease (Fig. 4). At diagnosis, however, 34.0% of patients with ATTRV30M amyloidosis in non-endemic areas and 30.0% of patients with non-V30M ATTR amyloidosis did not have an apparent family history of an affected patient or family members suspected of having the disease ( $P < 0.05$ ).

Sixty-three point six percent of patients with ATTRV30M amyloidosis in endemic areas presented with polyneuropathy as an initial manifestation. Patients with ATTRV30M amyloidosis in non-endemic areas initially had polyneuropathy (66.6%); patients with non-V30M ATTR amyloidosis initially developed polyneuropathy (27.5%), autonomic dysfunction, heart failure, arrhythmia, vitreous opacities, and/or cognitive impairment (Fig. 5). The frequency of

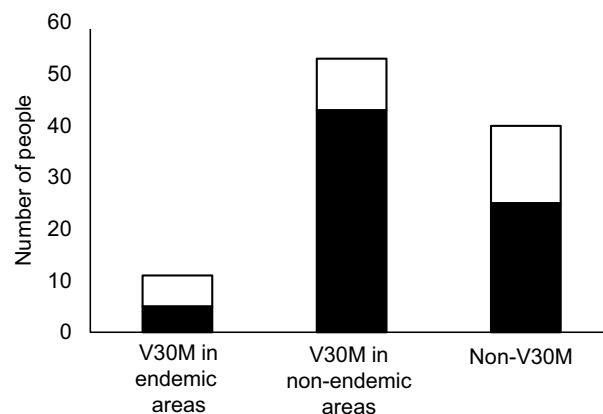


**Fig. 2** Age at disease onset. \* $P < 0.05$

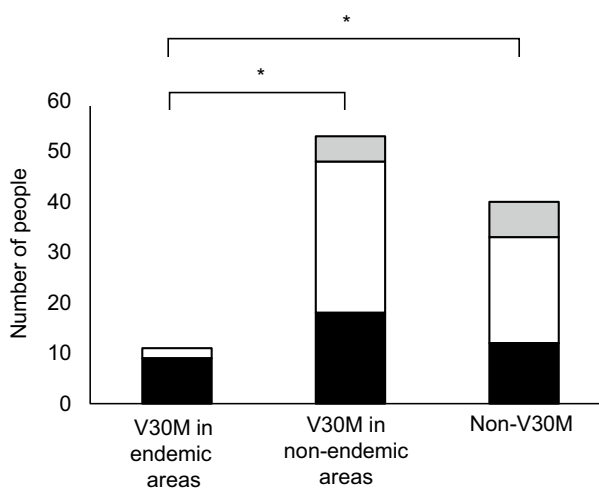
polyneuropathy as an initial manifestation of patients with ATTRV30M amyloidosis in endemic areas was significantly higher compared with that in patients with non-V30M ATTR amyloidosis ( $P < 0.01$ ).

The time from disease onset to diagnosis was  $2.6 \pm 1.7$  years (median 2.5, range 0.2–5.9) in endemic areas, whereas this value was  $3.6 \pm 2.4$  years (median 3.4, range 0.3–10.4) in patients with ATTRV30M amyloidosis in non-endemic areas and  $2.5 \pm 2.1$  years (median 2.0, range 0.1–8.4) in patients with non-V30M ATTR amyloidosis (Fig. 6).

Five patients with ATTRV30M amyloidosis in endemic areas underwent liver transplantation at the age of  $35.7 \pm 6.1$  (median 35.9, range 29.6–43.7) years, which



**Fig. 3** Male–female ratio. Black boxes indicate males and white boxes indicate females



**Fig. 4** Family history. Black boxes indicate those with a family history of disease, white boxes indicate those without a known family history of disease, and gray boxes indicate those with an unknown family history. \**P* < 0.05

was  $3.3 \pm 0.7$  years (median 3.0, range 2.8–4.6) after disease onset. One patient with ATTRV30M amyloidosis in non-endemic areas underwent liver transplantation at the age of 46.5 years, which was 2.4 years after disease onset. One patient with non-V30M ATTR (G47R) amyloidosis also underwent liver transplantation at the age of 49.7 years, which was 2.4 years after disease onset. All these patients survived.

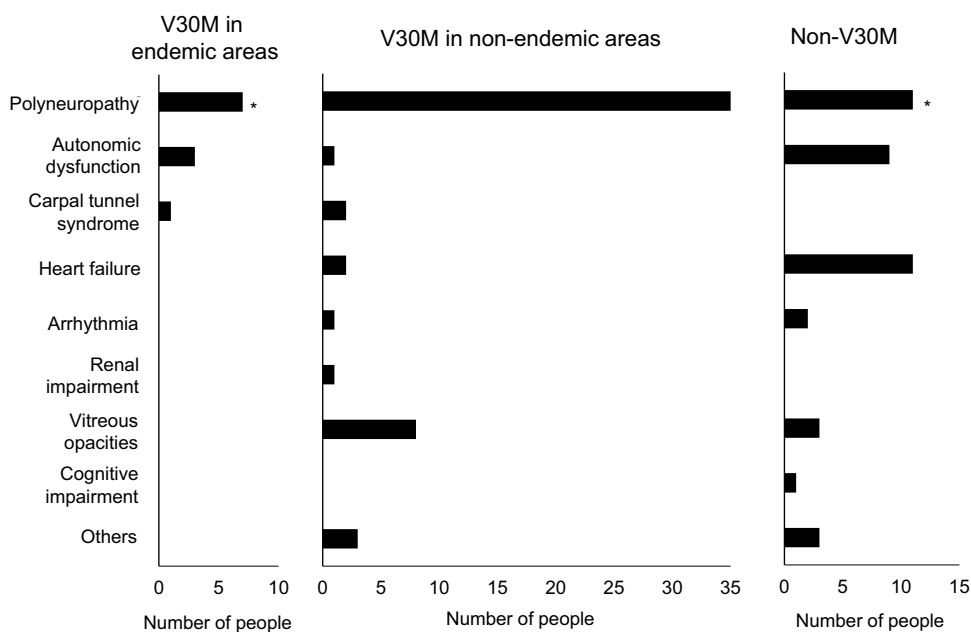
Twenty-four patients in endemic areas received a diagnosis of ATTRV30M amyloidosis during January 1, 2000, and March 31, 2012. The age at onset of

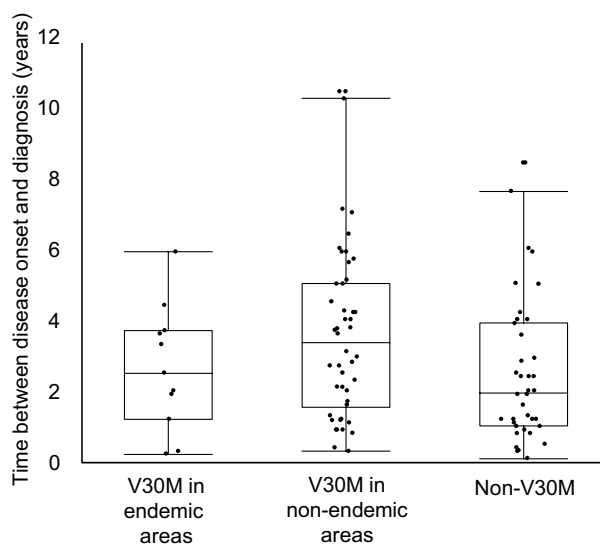
disease ( $36.7 \pm 11.4$  years; median 32.9, range 24.0–62.7), male–female ratio (0.41:1), presence of family history (100%), duration between disease onset and diagnosis ( $1.6 \pm 1.2$  years; median 1.2, range 0.1–3.9) of these 24 patients were not significantly different from those of patients diagnosed from April 1, 2014, to March 31, 2017. Of the 24 patients, 54, 21, and 25% presented with polyneuropathy, autonomic dysfunction, and gastrointestinal symptoms, respectively. Nineteen patients (5 male, 14 female) underwent liver transplantation at the age of  $35.4 \pm 6.5$  years (median 33.8, range 27.4–51.3), which was  $2.0 \pm 1.6$  years (median 1.4, range 0.6–5.7) after the onset of disease. Although the 10-year survival rate of the patients after the onset of disease was 100%, one patient died of chronic rejection at 10.8 years after disease onset (26.3 years old) and 5.0 years after liver transplantation (32.1 years old).

### Discussion

We demonstrated that patients with ATTRV30M amyloidosis in non-endemic areas and patients with non-V30M ATTR amyloidosis were more common than was previously believed. Patients with ATTRV30M amyloidosis in endemic areas demonstrated mainly polyneuropathy or autonomic disturbances as initial manifestations, a high penetrance, and an early age at disease onset, whereas patients with ATTRV30M amyloidosis in non-endemic areas manifested mainly polyneuropathy as an initial manifestation, an older age at disease onset (older than 50 years), and a low penetrance [21, 22]. Patients with non-V30M ATTR amyloidosis presented with various

**Fig. 5** Initial manifestations of hereditary ATTR amyloidosis. The frequency of polyneuropathy as an initial manifestation in patients with non-V30M ATTR was lower compared with the frequency in patients with ATTRV30M in endemic areas. \**P* < 0.05





**Fig. 6** Time between onset of disease and diagnosis

manifestations and had an older age at onset and a low penetrance. These differences in clinical characteristics may be related to the long time to reach a diagnosis of hereditary ATTR amyloidosis, especially in non-endemic areas [3].

More patients with hereditary ATTR amyloidosis may be present in non-endemic areas, in addition to patients with ATTRV30M amyloidosis in endemic areas, than previously expected [23]. Hereditary ATTR amyloidosis with the V30M mutation was previously thought to be a rare disease in endemic areas. However, because of the development of genetic analysis and the evidence from new cases, increasing numbers of patients with ATTRV30M amyloidosis in non-endemic areas and patients with non-V30M ATTR amyloidosis have been identified [24, 25].

This study showed that patients with the classic ATTRV30M amyloidosis mainly developed the disease at a relatively young age (< 50 years old) in endemic areas, but patients with ATTRV30M amyloidosis in non-endemic areas developed the disease at later ages and patients with non-V30M ATTR amyloidosis (various genotypes) developed the disease relatively late [26]. Patients with ATTRV30M amyloidosis reportedly developed the disease at early ages in endemic areas in Portugal and Japan, whereas they developed the disease at later ages in endemic areas in Sweden and in non-endemic areas in Japan [21, 27]. Although many studies of clinical cases reported the clinical manifestations including age at disease onset, well-designed studies had not yet been performed. Liver transplantation, which removes mutant TTR in the blood, is recommended for patients younger than 60 years, and this treatment was reportedly highly effective especially for those younger than 50 years [28–31]. Evidence for the effects of TTR stabilizers, gene

silencing treatments, and antibody therapies for early- and late-onset patients is expected in the future.

Patients with ATTRV30M amyloidosis in non-endemic areas and those with non-V30M ATTR amyloidosis showed a male predominance. The male–female ratio for patients with non-V30M ATTR amyloidosis was not previously well known. The male predominance of patients with ATTRV30M amyloidosis in non-endemic areas was reported previously (male–female ratio 4.4:1) [21]. Wild-type ATTR amyloidosis (senile systemic amyloidosis), presenting with bilateral carpal tunnel syndrome and heart failure with a preserved ejection fraction, also develops mainly in male patients, but the reason for this characteristic is not known [32, 33].

Because many sporadic cases in non-endemic areas had a diagnosis of hereditary ATTR amyloidosis but did not have known affected relatives, this disease should be part of the differential diagnosis in patients with persistent polyneuropathy, heart failure, or systemic disorders even if patients do not have a family history of the disease [18]. Several years after a late-onset proband who could have had de novo disease received a diagnosis of ATTRV30M amyloidosis in a non-endemic area, the disease developed in some family members. These cases suggest that the relatives may be carriers of mutant genes with incomplete penetrance.

Clinical manifestations of hereditary ATTR amyloidosis, which is caused by a single-gene abnormality, were diverse and related to genetic and environmental factors. Patients with ATTRV30M amyloidosis in endemic areas mainly showed polyneuropathy and autonomic disturbances, and patients with ATTRV30M amyloidosis in non-endemic areas primarily showed polyneuropathy, as reported previously [22, 34]. Patients with non-V30M ATTR amyloidosis had, in addition to the manifestations just mentioned, heart failure, vitreous opacities, or cognitive impairment as initial manifestations [35]. Phenotypic variations in hereditary ATTR amyloidosis may be related to variations in the production of mutant TTR as influenced by endoplasmic reticulum-assisted folding in competition with endoplasmic reticulum-associated degradation in hepatocytes, the stability of the tetramer in the blood, and the affinity of TTR for tissues in certain organs [36]. Also, Western blot analysis of amyloid deposits obtained from late-onset patients revealed fragmented TTR (49–127) and full-length TTR (1–127) (type A), whereas this analysis of amyloid deposits obtained from early-onset patients revealed only full-length TTR (type B), a result that suggests a difference in the amyloid fibrils according to phenotype [37].

Analysis of clinical manifestations at disease onset is useful for early diagnosis in clinical practice, which may lead to early intervention. Initial manifestations are also helpful for clinical studies of the phenotypes in each genotype. Polyneuropathy frequently developed in patients with ATTRV30M



amyloidosis, and less frequently developed in patients with non-V30M ATTR amyloidosis. Initial manifestations derive from organs in which amyloid is deposited, i.e., organs that are most susceptible to amyloid deposition, and may become the main manifestations during the clinical course of the disease.

Some of those patients had received intravenous immunoglobulin therapy for several years after being misdiagnosed as having chronic inflammatory demyelinating polyneuropathy [25, 38]. Protein levels in the cerebrospinal fluid can increase in this disease and in hereditary ATTR amyloidosis. Hereditary ATTR amyloidosis as well as amyloid light chain, apolipoprotein AI, gelsolin,  $\beta_2$ -microglobulin, and prion protein amyloidoses should be considered in the differential diagnosis for patients who do not respond to immunomodulatory treatments [25].

## Conclusions

In this study, we demonstrated that patients with hereditary ATTRV30M amyloidosis in non-endemic areas and patients with non-V30M ATTR amyloidosis occur more often than was previously believed. To facilitate early diagnosis and early intervention with disease-modifying therapies, greater understanding of hereditary ATTR amyloidosis and increased development of diagnostic tools for hereditary ATTR amyloidosis are needed.

## Compliance with ethical standards

**Conflicts of interest** The authors declare that they have no conflict of interest.

**Ethical standards** This Institutional Review Board of the Graduate School of Medical Sciences, Kumamoto University (No. 1172, 1387) approved this study.

**Informed consent** All patients gave their informed consent prior to their inclusion in this study.

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